UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,440	01/19/2000	DAVID PHILIP LANE	MEWB25.001AP	7276

20995 7590 03/31/2003

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/31/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,440	LANE, DAVID PHILIP	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *5-10 and 12-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *17* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-9, 11, species a peptide having a sequence corresponding to human p53, and cancer treatment in Paper Nos. 13 and 16 is acknowledged.

After review and reconsideration, the restriction requirement of paper Nos: 7 and 15 are vacated, and claims 1-27 require new restriction.

ELECTION/RESTRICTIONS

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

It is noted that the claims of the instant application have been determined to include linking claims 1, 11. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 1 and 11. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional

application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

This application contains claims directed to the following patentably distinct inventions linked by claims 1 and 11:

Group I. Claims 1-5, 11, drawn to a method for treating or preventing cancer, comprising administering an agent having the property of disrupting the binding of human p53 and mdm2, wherein said agent comprises a peptide having a sequence corresponding to human p53, or a peptide having a motif FxxxW (SEQ ID NO:4), where x is any amino acid.

Group II. Claims 1-2, 6-7, 11, drawn to a method for treating or preventing cancer, comprising disrupting the binding of human p53 and mdm2, using an antibody capable of blocking a p53 binding site of mdm2.

Group III. Claims 1-2, 8-9, 11, drawn to a method for treating or preventing cancer, comprising disrupting the binding of human p53 and mdm2, using an antibody capable of blocking mdm2 binding site of p53.

Group IV. Claims 1-5, 11, drawn to a method for treating or preventing a viral condition, comprising disrupting the binding of human p53 and mdm2, using an agent having the property of disrupting the binding of human p53 and mdm2 wherein said agent comprises a peptide having a sequence corresponding to

human p53, or a peptide having a motif FxxxW(SEQ ID NO:4), where x is any amino acid.

Group V. Claims 1-2, 6-7, 11, drawn to a method for treating or preventing a viral condition, comprising disrupting the binding of human p53 and mdm2, using an antibody capable of blocking a p53 binding site of mdm2.

Group VI. Claims 1-2, 8-9, 11, drawn to a method for treating or preventing a viral condition, comprising disrupting the binding of human p53 and mdm2, using an antibody capable of blocking mdm2 binding site of p53.

Group VII. Claims 1-5, 11, drawn to a method for treating or preventing a condition associated with non functional p53 or mdm2 other than cancer, or a viral condition, comprising disrupting the binding of human p53 and mdm2, using an agent having the property of disrupting the binding of human p53 and mdm2 wherein said agent comprises a peptide having a sequence corresponding to human p53, or a peptide having a motif FxxxW(SEQ ID NO:4), where x is any amino acid.

Group VIII. Claims 1-2, 6-7, 11, drawn to a method for treating or preventing a condition associated with non functional p53 or mdm2, other than cancer, or a viral condition, comprising disrupting the binding of human p53 and mdm2, using an antibody capable of blocking a p53 binding site of mdm2.

Group IX. Claims 1-2, 8-9, 11, drawn to a method for treating or preventing a condition associated with non functional p53 or mdm2 other than cancer, or a viral

condition, comprising disrupting the binding of human p53 and mdm2, using an antibody capable of blocking mdm2 binding site of p53.

Group X. Claims 1-2, 10-11, drawn to a method for treating or preventing cancer, comprising inhibiting the production of mdm2, using an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in a population of cells.

Group XI. Claims 1-2, 10-11, drawn to a method for treating or preventing a viral condition, comprising inhibiting the production of mdm2, using an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in a population of cells.

Group XII. Claims 1-2, 10-11, drawn to a method for treating or preventing a condition associated with non functional p53 or mdm2, other than cancer, or a viral condition, comprising inhibiting the production of mdm2, using an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in a population of cells.

Group XIII. Claims 12-16, drawn to a method of activating p53, comprising exposing a population of cells to an agent capable of disrupting the binding of human p53 and mdm2, wherein said agent is a peptide having a sequence corresponding to human p53, or a peptide having the motif FxxxW (SEQ ID NO:4), where x is any amino acid, wherein the cells do not overexpress mdm2.

Group XIV. Claims 12-13, 17-18, drawn to a method of activating p53, comprising exposing a population of cells to an agent capable of disrupting the binding of human p53 and mdm2, wherein said agent is an antibody capable of blocking a p53 binding site of mdm2, wherein the cells do not overexpress mdm2.

Group XV. Claims 12-13, 19-20, drawn to a method of activating p53, comprising exposing a population of cells to an agent capable of disrupting the binding of human p53 and mdm2, wherein said agent an antibody capable of blocking mdm2 binding site of p53, wherein the cells do not overexpress mdm2.

Group XVI. Claims 12, 21, drawn to a method of activating p53, comprising exposing a population of cells to an agent capable of inhibiting the production of mdm2, wherein the agent is an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in a population of cells, and wherein the cells do not overexpress mdm2.

Group XVII. Claims 22-27, drawn to a method for screening peptide test substances that disrupt the binding of human p53 and mdm2.

Group XVIII. Claim 22, 26-27, drawn to a method for screening antibodies that disrupt the binding of human p53 and mdm2, via blocking a p53 binding site of mdm2.

Group XIX. Claim 22, 26-27, drawn to a method for screening antibodies that disrupt the binding of human p53 and mdm2, via blocking mdm2 binding site of p53.

Group XX. Claims 22, 26-27, drawn to a method for screening test substances that inhibit the production of mdm2.

In addition, upon election of any of groups I-XII, further election of the following patentably distinct species is required:

Treating or preventing a condition.

Upon election of any of groups I, IV, VII, XIII, further election of the following patentably distinct species is required:

A peptide having a sequence corresponding to human p53, or a peptide having a motif FxxxW (SEQ ID NO:4), where x is any amino acid.

Upon election of any of groups XVII-XX, further election of the following patentably distinct species is required:

Microinjection into a cell or transport into cells.

The inventions listed as Groups I-XX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as groups I-XX do not relate to a single general inventive concept because they lack the same or corresponding technical feature. The technical feature of group I is administering an agent having the property of disrupting the binding of human p53 and mdm2 wherein said agent comprises a peptide having a sequence corresponding to human p53, or a peptide having a motif FxxxW (SEQ ID NO:4), where x is any amino acid. The agent having the property of disrupting the binding of human p53 and mdm2 wherein said agent comprises a peptide having a sequence "corresponding" to human p53, or a peptide having a motif FxxxW (SEQ ID NO:4), where x is any amino acid, is known in the art, which is the same as the peptides within the sequence of human p53, or the sequence FxxLW, for use in interruption of binding between mdm2 and p53,

comprising administering said peptide, as taught by WO 9602642A1, pages 5-6. Group I thus lacks novelty, and does not make a contribution over the prior art.

During a telephone conversation with Ginger Dredger on 02/06/03 a provisional election was made to elect group I, claims 1-4, 11, species "a peptide having a sequence corresponding to human p53" and species "treatment of cancer", with traverse. Affirmation of this election must be made by applicant in replying to this Office action. Claim 5 is withdrawn from consideration as being drawn to non-elected species. Claims 6-10, 12-27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Accordingly, group I, claims 1-4, 11, species "a peptide having a sequence corresponding to human p53" and species "treatment of cancer", are examined in the instant application.

OBJECTION

1. Claim 4 is objected to for the use of the language "a corresponding portion of human p53". It is not clear which corresponding portion of p53 is referred to.

2. Claims 3-5 are objected to for the use of the language "an amino sequence corresponding to human p53". It is not clear how the amino acid sequence corresponds to human p53.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 3-4 are drawn to a method for treating a condition associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, comprising administering an agent having the property of disrupting the binding of p53 and mdm2, wherein said agent comprises a peptide having an amino acid sequence corresponding to human p53, which has the property of binding to mdm2, or a peptide that is less than 25 amino acids in length, and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of p53.

The specification discloses peptides of SEQ ID NO:2 and 3, that are inserted into thioredoxin, are potent inhibitors of the interaction between p53 and mdm2 (p. 24-25 and figure 1).

It is noted that binding to mdm2 is not a function of the claimed peptide. It is further noted a peptide having an amino acid sequence "corresponding" to human p53,

which has the property of binding to mdm2 encompasses variants of p53, and unrelated sequences comprising a fragment of p53. In addition, it is noted that a peptide that is less than 25 amino acids in length, and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of p53 encompasses variants of any of p53 fragments.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification discloses variant peptides that differ from the wt. p53 sequence by one or more addition, substitution, deletion, and insertion of one or more amino acids, but which retains the binding of mdm2 (p.7, second paragraph). The "preferred" variants include the motif FxxxW, where x is any amino acid, and will "typically" share at least about 70%, 80%, 90% or 95% sequence identity with the corresponding portion of p53. No further description of variants is provided in the specification. The claims 3-4

however read on variants of p53 fragments, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. The claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the claims do not place any limit on the number of amino acids that could be substituted. Thus the scope of the claims includes numerous structural variants. Although the specification discloses that the types of changes are routinely done in the art, the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed peptide could function as contemplated. No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed variants are disclosed, because the function of a peptide sequence could be abolished, even with substitution of only one amino acid of the peptide (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In addition, although conservative substitution would not destroy the biological function of a peptide, the claims fails to disclose which amino acid(s) would be subjected to conservative substitution. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, SEQ ID NO:2 or 3 alone is

insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of variants. Thus, applicant was not in possession of the claimed variants.

Thus, there is insufficient support of claims 3-4 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore, only a method for treating a condition associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, comprising administering a peptide consisting of SEQ ID NO: 2 or 3, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1-4, 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-4, 11 are drawn to a method for treating a condition associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, wherein said condition is cancer, comprising administering an agent having the property of disrupting the binding of p53 and mdm2, wherein said agent comprises a peptide having an amino acid sequence corresponding to human p53, which has the property of binding to mdm2, or a peptide that is less than 25 amino acids in length, and has an amino acid

sequence having at least 70% amino acid sequence identity with a corresponding portion of p53.

The specification discloses peptide of SEQ ID NO:2 (TIP) or SEQ ID NO:3 (TIP 12/1), that are inserted into thioredoxin, wherein TIP wt contains the sequence corresponding to p53 wild type sequence P13 to N29, are potent inhibitors of the interaction between p53 and mdm2, as compared to the control thioredoxin lacking the peptide insertion (p. 24-25 and figure 1). The specification discloses that TIP is 50 times less potent than TIP 12/1 (p. 25, item 2). The specification discloses that microinjection of a plasmid containing TIP12/1 (SEQ ID NO:3) into a mouse prostate derived cell, having low level of p53 and mdm2 and transfected with p53 responsive beta-galactosidase reporter, strongly induces the p53 dependent reporter activity (p.27) .The specification further discloses co-transfection of a plamid containing said reporter, and a plasmid containing TIP12/1 (SEQ ID NO:3) into three different cell lines: 1) a breast cancer cell line MCF-7 which expresses low level of wt p53 and no reported mdm2 elevation (p.28, lines 5-7, and last paragraph), 2) an osteosarcoma cell line U2-OS, which expresses elevated levels of mdm2-mRNA, but without gene amplification for mdm2, and 3) a human osteosarcoma cell OSA, with elevated levels of mdm2 due to gene amplification for mdm2 (p.28, first, and last paragraph). The specification discloses that induction of p53 transcriptional activity is the highest, comparable with induction by UV, for the breast cancer cell line having undetectable levels of mdm2, as compared to the other two cell lines with elevated levels of mdm2 (p29 and figure 3). The specification contemplates that inhibitors of the interaction between mdm2 and p53 in

tumor cells expressing wt p53, which lead the way to induce p53 transcriptional activity, would potentially mimic the effect of common cancer treatments which induce the growth inhibitory and apoptotic properties of p53, by the induction of DNA damage without requiring the non specific consequences of this DNA damage (p.34).

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between increased transcriptional activity of p53 in transfected breast tumor cells with treating cancers *in vivo*. The *in vitro* experimental data presented is clearly not drawn to subjects with tumor cells, wherein in transfected cells the proteins of interests are artificially overexpressed, and could cause artificial protein-protein interaction, which is not the case with *in vivo* cancer conditions. Further, characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor

cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo.* These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo.* Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that,

petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -

type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, administration of the claimed peptides would be in any way correlated with an increase in p53 transcriptional activity in cancer cells. Further, even if the p53 transcriptional activity is increased in cancer cells *in vivo*, it is unpredictable that said increase would result in cell cycle arrest or cancer cell apoptosis due to well-known homeostasis regulation *in vivo*. Further, Haupt, Y et al, 1996, The EMBO J, 15(7): 1596-1606, IDS # 10, of paper No:6, on 09/19/200, teach that the particular cellular outcome in response to activated p53 depends on cell type, cellular context and extracellular signals, and that in some cases p53-mediated apoptosis can be inhibited by the presence of survival factors, including various cytokines (p. 1596, first column, briding second column). Moreover, even if the p53 transcriptional activity is increased in cancer cells *in vivo*, it is unpredictable that said increase would result in cancer treatment, because it is well known n the art that cancer treatment is unpredictable (see below).

Further, an anti-tumor peptide must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have an alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the anti-tumor peptide is transfected into the target cells and is artificially overexpressed in the cells during the entire exposure period. This is not the case *in vivo*, where exposure tat the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The peptide may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the peptide may not otherwise reach the targert because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the peptide has no effect, circulation into the target area may be insufficient to carry the peptide and a large enough local concentration may not be established.

Further, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones

promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that administration of a peptide having an amino acid sequence corresponding to human p53, or a peptide having at least 70% amino acid sequence identity with a corresponding portion of human human p53, or SEQ ID NO:3 would result in treatment of cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of

experimental evidence, no one skilled in the art would accept the assertion that that administration of a peptide having an amino acid sequence corresponding to human p53, or a peptide having at least 70% amino acid sequence identity with a corresponding portion of human human p53, or SEQ ID NO:3 would result in treatment of cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph, claims 1-4, 11 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cancers that do not express mdm2, comprising administering a peptide consisting of SEQ ID NO:3, does not reasonably provide enablement for a method for treating a condition associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, wherein said condition is cancer,

comprising administering an agent having the property of disrupting the binding of p53 and mdm2, wherein said agent comprises a peptide having an amino acid sequence "corresponding" to human p53, which has the property of binding to mdm2, or a peptide that is less than 25 amino acids in length, and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of p53. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-4, 11 are drawn to a method for treating a condition associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, or for cancer treatment, comprising administering an agent having the property of disrupting the binding of p53 and mdm2, wherein said agent comprises a peptide having an amino acid sequence "corresponding" to human p53, which has the property of binding to mdm2, or a peptide that is less than 25 amino acids in length, and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of p53.

It is noted that a peptide having an amino acid sequence "corresponding" to human p53 encompasses variants of human p53 that binds to mdm2.

It is further noted that a peptide that is less than 25 amino acids in length, and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of p53 encompasses a variant of any portion of human p53.

Applicants have not shown that the claimed variants are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

2. If Applicant could overcome the above 112, first paragraph, claims 1-4, 11 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cancers that do not express mdm2, comprising

administering a peptide consisting of SEQ ID NO:3, does not reasonably provide enablement for a method for treating "a condition associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed", or "cancer treatment", comprising administering an agent having the property of disrupting the binding of p53 and mdm2, wherein said agent comprises a peptide having an amino acid sequence corresponding to human p53, which has the property of binding to mdm2, or a peptide that is less than 25 amino acids in length, and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of p53. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-4, 11 are drawn to a method for treating "a condition" associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, or for "cancer" treatment, comprising administering an agent having the property of disrupting the binding of p53 and mdm2, wherein said agent comprises a peptide having an amino acid sequence corresponding to human p53, which has the property of binding to mdm2, or a peptide that is less than 25 amino acids in length, and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of p53.

The claims 1-4, 11 encompass a method for treating any condition associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, or for treatment of any cancer.

The specification discloses that microinjection of a plasmid containing TIP12/1 (SEQ ID NO:3) into a mouse prostate derived cell, having low level of p53 and mdm2 and transfected with p53 responsive beta-galactosidase reporter, strongly induces the p53 dependent reporter activity (p.27) .The specification further discloses transfection of a plasmid containing TIP12/1 (SEQ ID NO:3) into three different cell lines: 1) a breast cancer cell line MCF-7 which expresses low level of wt p53 and no reported mdm2 elevation (p.28, lines 5-7, and last paragraph), 2) an osteosarcoma cell line U2-OS, which expresses elevated levels of mdm2-mRNA, but without gene amplification for mdm2, and 3) a human osteosarcoma cell OSA, with elevated levels of mdm2 due to gene amplification for mdm2 (p.28, first, and last paragraph). The specification discloses that induction of p53 transcriptional activity is the highest, comparable with induction by UV, for the breast cancer cell line having undetectable levels of mdm2, as compared to the other two cell lines with elevated levels of mdm2 (p29 and figure 3).

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between a breast cancer cell line that has undetectable level of mdm2 with any disease condition that is associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed. The specification does not disclose which diseases are associated with the binding of mdm2 to p53 in cells in which mdm2 is not overexpressed, and how to treat said diseases.

Further, one cannot extrapolate treating cancers that do not express mdm2 with treating any cancer. It is unpredictable that any cancer would not express mdm2, because different cancers have different etiology and properties.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/02642A1 (IDS # 2 of paper No:6, on 09/19/200).

Claim 11 is drawn to a method for cancer treatment, comprising administering an agent having the property of disrupting the binding of p53 and mdm2.

WO 96/02642A1 discloses interruption of binding of mdm2 and p53 protein, and therapeutic application thereof, including treatment of tumors (abstract). WO 96/02642A1 discloses administering a peptide which is able to disrupt or prevent the binding between p53 and mdm2 (p.5, second paragraph).

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

The figure legend of figure 1 recites sequences that are not accompanied with sequence identification numbers.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

February 20, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER